The Patent Office
Concept House
Cardiff Road
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NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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Signed R. Mahon

Dated 21 November 2003

PRIORITY DOCUMENT
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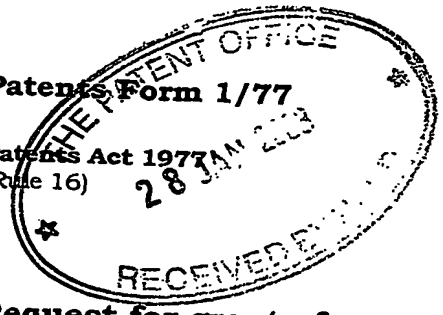
Patents Form 1/77

Patents Act 1977
(Rule 16)



The **Patent Office**

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP10 8QQ

1. Your reference — **G-32539P1/ABR 9924**

2. Patent application number
(The Patent Office will fill in this part)
29JAN03 E780518-1 000524
P01/7700 0.00-0301938.7

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*
BIOCHEMIE GESELLSCHAFT MBH
A-6250 KUNDL, TIROL
AUSTRIA

Patent ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — **AUSTRIA**

0301938.7
28 JAN 2003
00339911001

4. Title of invention — **Organic compounds**

5. Name of your agent *(If you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

~~B.A. YORKE & CO.~~
~~CHARTERED PATENT AGENTS~~
~~COOMB HOUSE, 7 ST. JOHN'S ROAD~~
~~ISLEWORTH~~
~~MIDDLESEX TW7 6NH~~
Novartis Pharmaceuticals UK Ltd
Patents and Trademarks
Wimblehurst Road
HORSHAM
West Sussex
RH12 5AB

Global Pin 373

Patents ADP number *(if you know it)* — **1800001** ADP No **0718522002**

6. If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day/month/year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

(see note (d))

Yes

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	**24**
Claim(s)	**2**
Abstract	**1**
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	**One**
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature Date

B.A. Yorke & Co. **28 January 2003**

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. J. Crook
020 8560 5847

Warning

After an application for a patent has been filed. the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the united Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) Once you have filled in the form you must remember to sign and date it.

e) For details of the fee and ways to pay please contact the Patent Office.

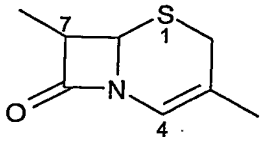
Organic compounds

The present invention relates to organic compounds which are β-lactam antibiotics or cephalosporins.

In one aspect the present invention provides a carboxylic acid ester of a pharmaceutically active compound having a carboxylic acid group –COOH as a part of its chemical structure, which ester is selected from the group consisting of 1-(1,3-disubstituted propoxycarbonyl-oxy)-ethyl carboxylic acid ester, 1-(2,3)-disubstituted propoxycarbonyloxy)-ethyl carboxylic acid ester, 1-(9H-fluorene-9-yl-(C_{1-4})alkanyloxycarbonyloxy)-ethyl carboxylic acid ester, 1-(decahydro-naphthalene-2-yl-oxycarbonyloxy)-ethyl carboxylic acid ester and 1-(2-amino (C_{1-6})alkoxy-carbonyloxy)-ethyl carboxylic acid ester.

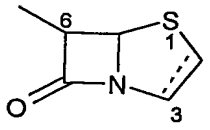
In a preferred aspect the pharmaceutically active compound is an antibiotic, e.g. selected from the group consisting of β-lactam antibiotics or cephalosporins.

In another referred aspect said carboxylic group is attached in position 4 of the azabicyclo-[4,2,0]octene ring structure of a cephalosporin of formula



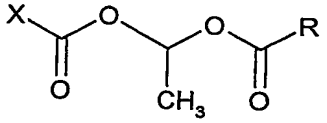
I

or said carboxylic group is attached in position 3 of the azabicyclo-[3,2,0]heptene ring structure of a penicillin of formula



II

In a preferred aspect the ester is an ester of the carboxyl group -COOH of formula



III

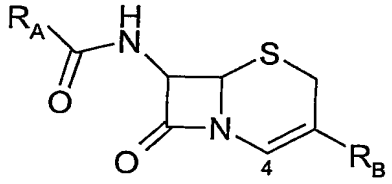
wherein X is a compound of formula I or II and R is

- a mono-or disubstituted 1-propoxy or 2-propoxy substituted with OH and/or (C_{1-22})alkyl-carbonyloxy,

- 9H-fluorene-9-yl-(C_{1-4})alkoxy,
- decahydronaphthoxy or
- amino(C_{1-6})alkoxy.

In another aspect the carboxylic acid ester is an ester selected from the group consisting of 1-(2,3,-dihydroxy-propoxycarbonyloxy)-ethyl carboxylic acid ester, 1-(2,3-diacetoxy-propoxycarbonyloxy)-ethyl carboxylic acid ester, 1-(3-acetoxy-2-octanoyl-oxy-propoxy-carbonyloxy)-ethyl carboxylic acid ester, 1-(2-acetoxy-3-octanoyloxy-propoxy-carbonyloxy)-ethyl carboxylic acid ester, 1-(2-acetoxy-1-acetoxymethyl-ethoxy-carbonyloxy)-ethyl carboxylic acid ester, 1-(9H-fluorene-9-yl-methoxycarbonyloxy)-ethyl carboxylic acid ester, 1-(9H-fluorene-9-yl-ethoxycarbonyloxy)-ethyl carboxylic acid ester, 1-(decahydro-naphthalene-2-yl-oxycarbonyloxy)-ethyl carboxylic acid ester and 1-(2-amino-ethoxy-carbonyloxy)-ethyl carboxylic acid ester of the carboxylic acid attached in position 4 of the ring structure of a cephalosporin of formula I or of the carboxylic acid attached in position 3 of the ring structure of a penicillin of formula II.

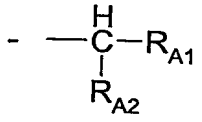
In a preferred aspect the carboxylic acid ester is an ester of the carboxcylic group attached in position 4 of a compound of formula



IA

wherein

R_A is a group of formula



wherein

R_{A1} is unsubstituted or one- or morefold substituted

- (C_{6-18})aryl, e.g. phenyl, or - (C_{6-18})aryl anellated with another ring system, e.g. naphthyl or benzothiophene
- (C_{3-8})cycloalkyl or (C_{3-8})cycloalkenyl or
- heterocyclyl.

R_{A2} is

- hydrogen, hydroxyl or hydroxycarbonyloxy
- unsubstituted or substituted amino, e.g. substituted by NH-CO-heterocyclyl
- sulfonyl, carbonyl or oxy-carbonyl-amino(C_{1-4})alkyl

or

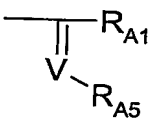
- $-(CH_2)_n-R_{A3}$

wherein R_{A3} is

- S-R_{A4} wherein R_{A4} is hydrogen or (C_{1-4})alkyl
- CN or
- COOH and

n is 1 to 6

or

- 

wherein

V is N or CH

R_{A1} is as defined above and

R_{A5} is unsubstituted or substituted hydroxyl, (C_{1-4})alkyl, (C_{1-4})alkenyl, (C_{1-4})alkoxy, e.g. (C_{1-4})alkoxy substituted by halogen carbonyloxy(C_{1-4})alkoxy, (C_{1-4})alkenyloxy, arylcarbonyloxy, arylcarbonyloxy, heterocyclyl or heterocyclylcarbonyloxy.

and

R_B is a group of formula

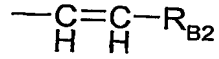
- $-(CH_2)_n-R_{B1}$

wherein R_{B1} is

- hydrogen, halogen or hydroxyl,
- unsubstituted or one- or morefold substituted

(C_{1-4})alkyl, (C_{1-4})alkoxy, amino(C_{1-4})alkyl, (C_{1-4})alkylcarbonyloxy, aminocarbonyl or phenyl,

or

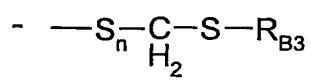
- 

wherein R_{B2} is

- hydrogen or hydroxyl,
- unsubstituted or one- or morefold substituted

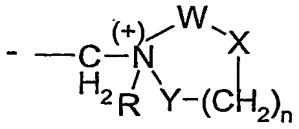
(C_{1-4})alkyl, amino(C_{1-4})alkyl, phenyl or heterocyclyl, which is a 5 or 6-membered heterocyclic ring system having 1 to 4 heteroatoms selected from N, O or S. Preferably the heterocyclyl is a 5 or 6 membered ring system having 1 or 2 heteroatoms selected from N or O.

or



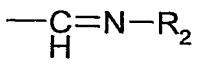
wherein R_{B3} is unsubstituted or one- or morefold substituted heterocyclyl or heterocyclylcarbonyl and n is o or 1

or



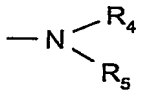
wherein X, Y and W independently of each other are C, CH, CH_2 or N, R is not present or is present and is (C_{1-4})alkyl and n is 1 to 6

or



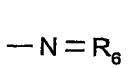
of formula I of claim 1 of **WO9635692,** wherein

R_2 denotes a group of formula



IIb

or

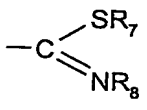


IIc

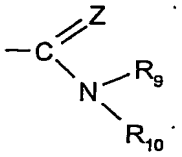
wherein

R_4 denotes hydrogen, phenyl, cycloalkyl or lower alkyl

R_5 denotes hydrogen, lower alkyl, heterocyclyl or a group of formulae

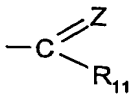


IId



IIe

or



IIf

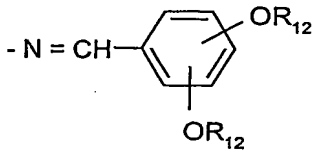
wherein

R_7 denotes lower alkyl

R_8 denotes hydrogen, cycloalkyl or lower alkyl

R_9 denotes hydrogen or lower alkyl,

R_{10} denotes hydrogen, hydroxy; amino; phenyl; alkenyl; cycloalkyl; heterocyclyl; unsubstituted alkyl; substituted alkyl, by CF_3, OH, alkoxy, carboxyl, halogen, amino, monoalkylamino, dialkylamino, trialkylamino, pyridyl or a a sulfonic acid residue; a group of formula



wherein

R_{12} denotes hydrogen or lower alkyl,

Z denotes oxygen, sulphur, or N-R_{13}, wherein

R_{13} denotes hydrogen or lower alkyl, and

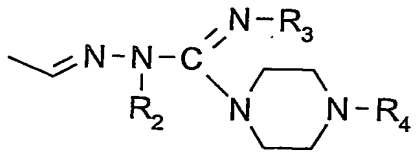
R_{11} denotes hydrogen; dihydroxyphenyl; cycloalkyl; heterocyclyl; unsubstituted lower alkyl; substituted lower alkyl by pyridyl or monoalkylamino, dialkylamino or trialkylamino; and,

R_4 and R_5 and/or R_9 and R_{10} independently of one another together with the nitrogen denote heterocyclyl,

R_6 denotes heterocyclyl, and

R_3 denotes hydrogen; acyl; carboxyl; unsubstituted alkyl; substituted alkyl by halogen or carboxyl

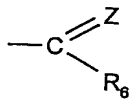
or



of formula I of claim 1 of **WO 9843981**, wherein

R_2 and R_3 are the same or different and independently of each other denote hydrogen, cycloalkyl, alkyl, alkenyl or alkinyl;

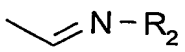
R_4 denotes hydrogen or a group of formula



wherein R_6 denotes amino, hydrazino aminoalkylamino, alkoxy, aryl, cycloalkyl, aryloxy, heterocyclyl, alkyl, alkenyl, alkinyl;

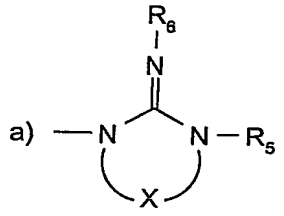
Z denotes O, S or NR_7, wherein R_7 is as defined as R_2;

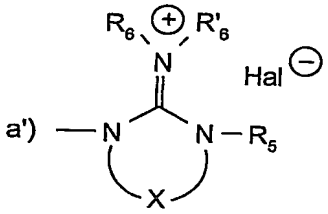
or

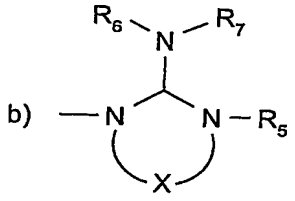


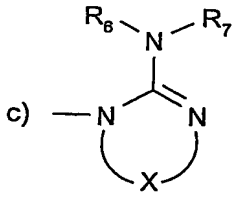
of a compound I of claim I of **WO9948896**, wherein

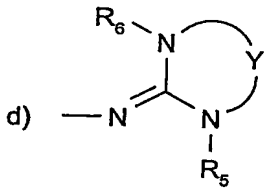
R_2 denotes a group of formula

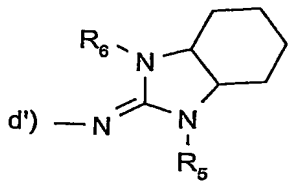


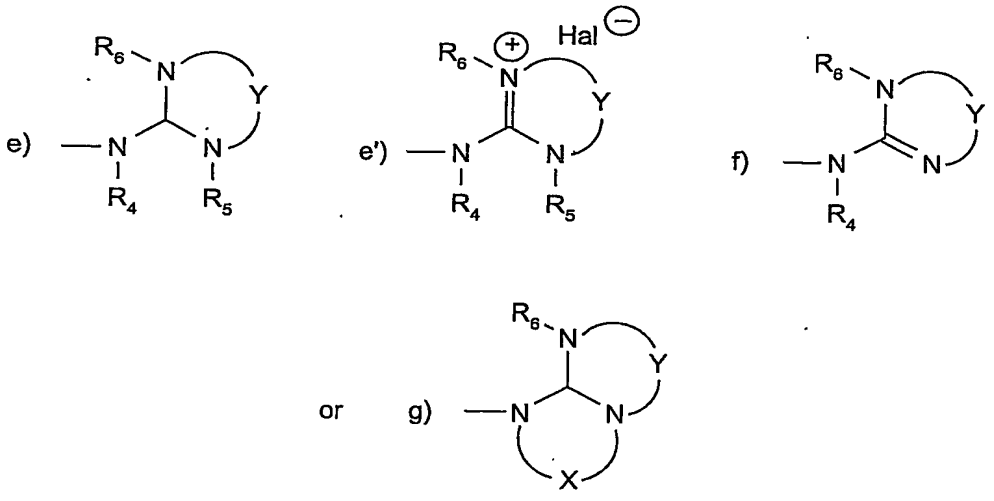












wherein

X and Y independently of each other each denote (C_{2-5})alkylene, or (C_{2-5})alkenylene wherein one -C=C- double bond is present, or, in case of at least C_4-alkenylene, wherein two -C=C- double bonds are present,

R_4 denotes hydrogen or alkyl,

R_5 denotes hydrogen, alkyl, or aminoiminomethyl,

R_6 denotes hydrogen, alkyl, cycloalkyl, amino, hydroxy, alkoxy, heterocyclyl or a group of formula -N=CHR_8, wherein

R_8 denotes alkyl, aryl or heterocyclyl, or

R_5 and R_6 together with the nitrogen atoms to which they are attached denote heterocyclyl,

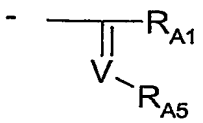
R'$_6$ denotes alkyl,

R_7 denotes hydrogen, or

R_6 and R_7 together with the nitrogen atom to which they are attached form heterocyclyl.

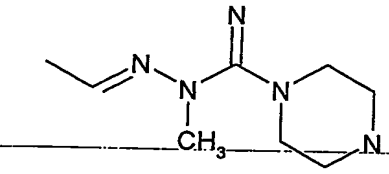
In a preferred aspect the carboxylic acid esters are esters of a compound of formula IA, wherein

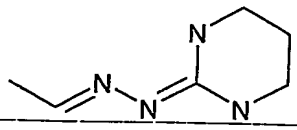
R_A is a group of formula

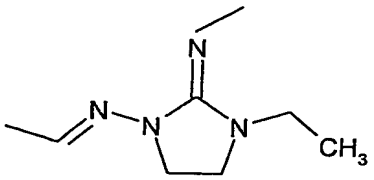


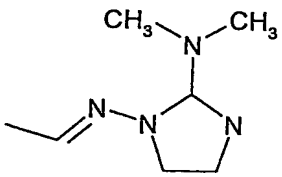
wherein V is N, R_{A5} is $-OCH_2F$ and

R_B is a group of formula









"Heterocyclyl" in the meaning of R_A includes a ring system having 5 or 6 ring members and 1 to 4 heteroatoms selected from N, O or S, which may be wholly or partly saturated, e.g. at least one N, which heterocyclyl is optionally anellated with another ring (system), e.g. wherein substituents are selected from hydroxyl, (C_{1-4})alkyl, (C_{1-4})alkoxy, amino(C_{1-4})alkyl, aminocarbonyl, (C_{1-4})alkoxyimino, imino(C_{1-4})oxyalkyl, imino(C_{1-4})oxy-carbonyloxyalkyl or imino-halo(C_{1-4})alkyl.

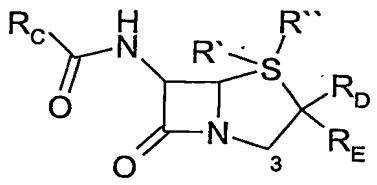
Heterocyclyl in the meaning of R_A preferably is pyrrolyl, imidazolyl, benzimidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, oxazolyl, thiophenyl, azolyl, thiazolyl, triazolyl, benzothiohenyl, furyl, and tetrazolyl; and may be unsubstituted or substituted by one or more, especially one or two, substitutents selected from the group as indicated above.

"Heterocyclyl" in the meaning of R_B includes a ring system having 5 or 6 ring members and 1 to 4 heteroatoms selected from N, O or S, which may be wholly or partly saturated, e.g. at least one N, which heterocyclyl is optionally anellated with another ring (system), e.g. wherein substituents are selected from hydroxyl, (C_{1-4})alkyl, (C_{2-6})alkenyl (C_{1-4})alkoxy, amino(C_{1-4})alkyl, carboxy(C_{1-4})alkyl, amino(C_{2-6})alkenyl or aminocarbonyl.

Heterocyclyl in the meaning of R_B preferably is pyrrolyl, imidazolyl, benzimidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, thidiazinyl, triazolyl, tetrazolo-pyridazinyl, triazyl-one and tetrazolyl; and may be nsubstituted or substituted by one or more, especially one or two, substitutents selected from the group as indicated above.

In another aspect the cephalosporin of formula IA is cefacetrile, cefaclor, cefadroxil, cefalexin, cefaloglycin, cefaloridine, cefalotin, cefamandole, cefapirin, cefatrizine, cefazedone, cefazolin, cefbuperazone, cefcapene, cefcanel, cefclidin, cefdinir, cefditoren, cefedrolor, cefempidone, cefepime, cefetecol, cefetamet, cefivitril, cefixime, cefluprenam, cefmatilen, cefmenoxime, cefmepidium, cefmetazole, cefminox, cefoperazone, cefodizime, cefpodoxime, cefonicid, cefoperazone, ceforanide, cefoselis, cefotaxime, cefotetan, cefotiam, cefoxitin, cefozopran, cefpimizole, cefluprenam, cefoxazol, cefoxitin, cefpiramide, cefprozil, cefquinome, cefradine, cefpirome, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephabacin, cephamycin A und B und C, chitinovorin, deoxycephamicin B or desacetoxy-cephalosporin C (also as a carbamate).

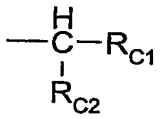
In another preferred aspect the the carboxylic acid ester is an ester of the carboxcylic group attached in position 3 of a compound of formula



IIA

wherein

R_C is a group of formula



wherein

R_{C1} is (C_{6-18})aryl, e.g. phenyl, or heterocyclyl, e.g. thiophenyl,

R_{C2} is carboxyl, sulfonyl, heterocyclyloxycarbonyl, amino or substituted amino, e.g. amino substituted by heterocyclylcarbonyl, amino(C_{1-4})alkylcarbonyl,

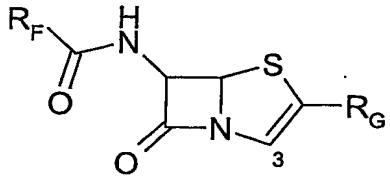
R_D and R_E independently of each other are (C_{1-4})alkyl, e.g. methyl, and

R` and R`` are present or not and when present are =O.

"Heterocyclyl" in the meaning of R_{C2} includes a ring system having 5 or 6 ring members and 1 to 4 heteroatoms selected from N, O or S, which may be wholly or partly saturated, e.g. at least one N, which heterocyclyl is optionally anelllated with another ring (system), e.g.

wherein substituents are selected from hydroxyl, (C_{1-4})alkyl, (C_{2-6})alkenyl (C_{1-4})alkoxy, amino(C_{1-4})alkyl, carboxy(C_{1-4})alkyl or aminocarbonyl.
Heterocyclyl in the meaning of R_{C2} preferably is thienyl and may be unsubstituted or substituted by one or more, especially one or two, substitutents selected from the group as indicated above.

In another preferred aspect the the carboxylic acid ester is an ester of the carboxcylic group attached in position 3 of a compound of formula



IIB

wherein
R_F is (C_{1-4})alkyl or substituted (C_{1-4})alkyl, e.g. substituted by OH, such as 1-ethanol, and
R_G is heterocyclyl.

"Heterocyclyl" in the meaning of R_G includes a ring system having 5 or 6 ring members and 1 to 4 heteroatoms selected from N, O or S, which may be wholly or partly saturated, e.g. at least one N, which heterocyclyl is optionally anelllated with another ring (system), e.g. wherein substituents are selected from hydroxyl, (C_{1-4})alkyl, (C_{2-6})alkenyl (C_{1-4})alkoxy, amino(C_{1-4})alkyl, carboxy(C_{1-4})alkyl, (C_{1-4})alkylaminocarbonyl or aminocarbonyl.
Heterocyclyl in the meaning of R_G preferably is pyrrolyl or furyl; and may be unsubstituted or substituted by one or more, especially one or two, substitutents selected from the group as indicated above.

In another aspect the penicillin of formula IIA is adicillin, almecillin, amdinocillin, amoxicillin, ampicillin, apalcillin, aspoxicillin, azidocillin, azlocillin, bacampicillin, bacmecillinam, benpenolisin, benzylpenicillin, bisnorpiperacillin, carbenicillin, carindacillin, carfecillin, ciclacillin, clometocillin, cloxacillin, dicloxacillin, epicillin, ertapenem, fenbenicillin, fibracillin, flucloxacillin, fomidacillin, fropenem = faropenem; furopenem; sufropenem sodium fumoxicillin, fuzlocillin, hetacillin, lenampicillin, levopropicillin, libecillide, mecillinam, meropenem, metampicillin, meticillin, mezlocillin, nafcillin, N-acetylisopenicillin N, oxacillin, penamecillin, penethacillin, penicillin K, penicillin G, penicillin S, penicillin V, penicillin X, penimepicyclin, penimocyclin, pheneticillin, phenoxymethylpenicillin, piperacillin, piroxicillin,

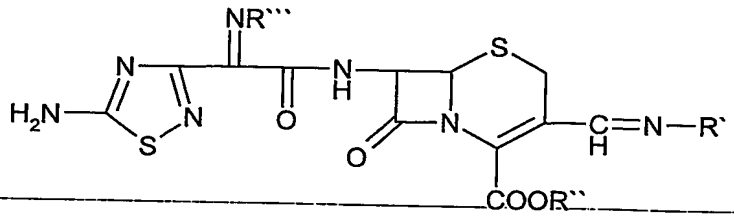
pivampicillin, pivmecillinam, prazocillin, propicillin, quinacillin, sulbactam, sulbenicillin, sultamicillin (as e.g. tosilate, besilate, closilate, napsilate), talampicillin, tazobactam-piperacillin, temocillin or ticarcillin.

A compound of formula I or II may be in the form of an physiologically-hydrolysable and -acceptable ester. By physiologically-hydrolysable and -acceptable esters as used herein is meant an ester in which the COO- group is esterified and which is hydrolysable under physiological conditions to yield an acid which is itself physiologically tolerable at dosages to be administered. The term is thus to be understood as defining regular pro-drug forms. An ester moiety may be preferably a group which is easily hydrolysable under physiological conditions. Such esters may be administered preferably orally. Parenteral administration may be indicated if the ester *per se* is an active compound or, if hydrolysis occurs in the blood.

Compounds provided by the present invention are hereinafter designated as "compound(s) of the present invention". A compound of the present invention includes a compound in any form, e.g. in the form of a salt, in free base form or in the form of a solvate. The present invention thus includes a compound in free base form or, e.g. where such forms exist, in the form of a salt, for example in the form of an acid addition salt, inner salt, quaternary salt, and/or in the form of a solvate, for example in the form of a hydrate. A salt may be a pharmaceutically acceptable salt of a compound of formula I or II such as a metal salt or an amine salt. Metal salts include for example sodium, potassium, calcium, barium, zinc, aluminum salts, preferably sodium or potassium salts. Amine salts include for example trialkylamine, procaine, dibenzylamine and benzylamine salts. A free form of a compound of formula I or II may be converted into a salt/solvate form and *vice versa*.

In a further aspect the present invention provides a compound of formula I or II in the form of a salt and/or a compound of formula I or II in the form of a solvate.

The present invention includes a compound of formula I or II in any isomeric from in which it may exist, e.g. optical isomers, stereoisomeric forms, cis-trans conformers, and mixtures thereof. E.g. the configuration of $-C=NR_3$ in a compound of formula



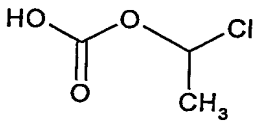
Ia

may be syn [(Z)] and anti [(E)] and is preferably syn [(Z)]. E.g. geometric isomers may be obtained, e.g. during a production process of a compound of formula I or II. E.g. a chiral carbon atom may be introduced, e.g. during a production process of a compound of formula I or II and corresponding stereoisomeric forms of a compound of formula I or II may be obtained, e.g a mixture of the individual stereoisomers, e.g. a racemate, or pure isostereoisomeric forms. Mixtures of isomers may be separated.

The present invention includes a compound of formula I or II in any tautomeric form.

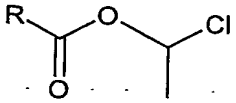
In another aspect the present invention provides a process for the production of a carboxylic acid ester of claim 1 comprising the steps

a. reacting a compound of formula R-OH wherein R is as defined above with a compound of formula



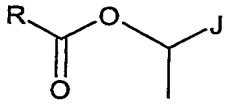
IV

to obtain a compound of formula



V

b. reacting a compound of formula V with NaJ to obtain a compound of formula



VI

and

c. reacting a compound of formula VI with X, which is a compound of formula I or II to obtain a compound of the present invention.

In a preferred aspect a compound of the present invention is obtained in reacting X, which is compound of formula I or II as indicated above with a compound of formula VI.

Any compound described herein, e.g. a compound of the present invention, may be prepared as appropriate, e.g. according to a method as conventional, e.g. or as specified herein.

If desired, reactive groups in starting materials may be protected with protecting groups, which may be or which are split off under the reaction conditions or after termination of the reaction. A compound of formula I or II may be isolated from the reaction mixture as appropriate, e.g. according to a method as conventional.

The compounds of formula I or II including salt/solvate, hereinafter designated as "active compound(s) of the invention" exhibits pharmacological activity, e.g. beside low toxicity and are therefore useful as pharmaceuticals. In particular, the active compounds of the invention show antimicrobial, *e.g.* antibacterial, activity against e.g. gram negative and gram positive bacteria, e.g. gram positive bacteria such as Escherichia, e.g. Escherichia coli; Enterobacter, e.g. Enterobacter cloacae; Enterococcus, e.g. Enterococcus faecalis; Klebsiella, e.g. Klebsiella pneumoniae; Streptococcus, e.g. Streptococcus pneuminiae; Staphylococcus, e.g. Staphylococcus aureus; and Pseudomonas, e.g. Pseudomonas aeruginosa, in vitro in the Agar Dilution Test according to National Commitee for Clinical Laboratory Standards (NCCLS) 1993, Document M7-A3Vol.13, No. 25: "Methods for dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Third Edition, Approved Standard". The active compounds show an MIC (µg/ml) in the Agar Dilution Test from about <6.4 to about >0.0125. The active compounds of the invention show an surprising overall activity spectrum.

The active compounds of the present invention in the form of a salt exhibit the same order of activity as the active compounds of the present invention in free form; optionally in the form of a solvate.

In another aspect the present invention provides an active compound for use as a pharmaceutical, preferably as an antimicrobial agent, such as an antibiotic.

In a further aspect the present invention provides an active compound of the present invention for use in the preparation of a medicament for the treatment of microbial diseases,

for example of diseases caused by bacterias selected from *Escherichia, Enterobacter, Enterococcus, Klebsiella, Streptococcus, Staphylococcus and Pseudomonas.* Treatment includes disease treatment and prophylactic treatment.

In a further aspect the present invention provides a method of treatment of microbial diseases which comprises administering to a subject in need of such treatment an effective amount of an active compound of the present invention.
For this indication, the appropriate dosage will, of course, vary depending upon, for example, the compound of formula I or II employed, the host, the mode of administration and the nature and severity of the conditions being treated. However, in general, for satisfactory results in larger mammals, for example humans, an indicated daily dosage is in the range from about 0.05 to 5 g, for example 0.1 to about 2.5 g, of an active compound of the invention conveniently administered, for example, in divided doses up to four times a day. An active compound of the invention may be administered by any conventional route, for example orally, *e.g.* in form of tablets or capsules, or parenterally in the form of injectable solutions or suspensions, e.g. in analogous manner to ceftazidime.

Because of the compounds activity against various e.g. bacterial strains, compounds of formula I or II are indicated for the treatment of microbial diseases, e.g. bacterial diseases. The compounds of the invention may be administered to larger mammals, for example humans, by similar modes of administration at similar dosages than conventionally employed with ceftazidime.

The compound of formula I or II may be administered in pharmaceutically acceptable salt form, *e.g.* acid addition salt form or base addition salt form or in the corresponding free forms, optionally in solvate form. Such salts exhibit the same order of activity as the free forms.

The present invention also provides pharmaceutical compositions comprising an active compound of the present invention in association with at least one pharmaceutically acceptable excipient, e.g. carrier or diluent. Such compositions may be manufactured accordingly, e.g. analogously to a method as conventional.

In the following examples all temperatures are given in degree centigrade and are uncorrected. RT means room temperature.

EXAMPLES

Example 1:

a) Carbonic acid 1-chloro-ethyl ester 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester

To 24 g of (2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol in 450 ml of dichloromethane 20.3 g of 4-methylmorpholine, 230 mg of 4-dimethylaminopyridine and 26.1 g of chloroformic acid 1-chloro-ethyl ester are added at 4°C. The mixture is stirred, a salt precipitated is filtered off and after chromatography carbonic acid 1-chloro-ethyl ester 2,2-dimethyl-[1,3]dioxolan-4-yl-methyl ester is obtained.

^{1}H-NMR ($CDCl_3$): 1.36 (s, 3H); 1.43 (2xs,3H); 1.83 (d, 3H, J=6Hz); 3.79 (m, 1H); 4.09 (m, 1H); 4.23 (m, 2H); 4.34 (m, 1H); 6.42 (q, 1H, J=6Hz)

b) Carbonic acid 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester 1-iodo-ethyl ester

To 151,2 g of sodium iodide in 1.25 l of acetonitrile 40 g of carbonic acid 1-chloro-ethyl ester 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester in 300 ml of acetonitrile are added. The mixture is stirred, a salt precipitated is filtered off and dissolved in ether. After washing solvent is evaporated and Carbonic acid 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester 1-iodo-ethyl ester is obtained.

^{1}H-NMR ($CDCl_3$): 1.36 (s,3H); 1.44 (2xs, 3H); 2.25 (2xd, 3H, J=6Hz); 3.78 (m, 1H); 4.09 (m, 1H); 4.22 (m, 2H); 4.33 (m, 1H); 6.75 (m, 1H,)

c) 7-{2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-(fluoromethoxyimino)-acetylamino}-3-formyl-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 1-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxycarbonyloxy)-ethyl ester

To 41.5 g of 7-{2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-[(Z)-fluoromethoxyimino]-acetylamino}-3-formyl-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt in 840 ml of dimethylacetamide 38 g of carbonic acid 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester 1-iodo-ethyl ester in 200 ml of dimethylacetamide are added. A reaction mixture formed is stirred, poured into 2 l of an ice-water mixture and extracted with ethylacetate. An organic layer is washed with saturated sodium bicarbonate solution, brine, dried, concentrated and a residue formed is triturated with ether. 7-{2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-(fluoromethoxyimino)-acetylamino}-3-formyl-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 1-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxycarbonyloxy)-ethyl ester is obtained.

^{1}H-NMR (DMSO-d_6): 1.22 (s, 3H); 1.30 (2xs, 3H); 1.56 (d, 3H, J=6Hz); 3.45 (d, 1H, J=18Hz); 3.64-4.30 (m, 6H); 5.33 (2xd, 1H, J=5Hz); 5.68 (m, 1H); 5.83 (m, 1H), 6.05 (2xdd, 1H, J=5Hz, 8Hz); 6.90/6.97 (2xq, 1H, J=6Hz); 8.20 (s, 1H); 9.62 (d, 1H, J=6Hz); 9.84 (d, 1H, J=8Hz)

Example 2:

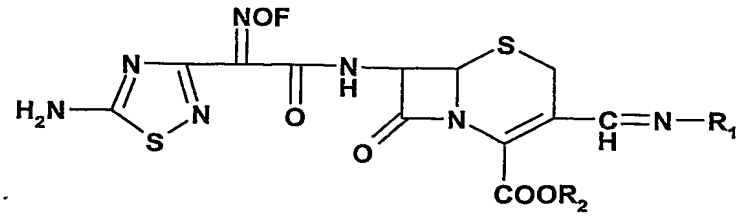
7-{2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-(fluoromethoxyimino)-acetylamino}-3-[methyl-(imino-piperazin-1-yl-methyl)-hydrazonomethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 1-(2,3-dihydroxy-propoxycarbonyloxy)-ethyl ester

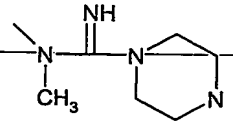
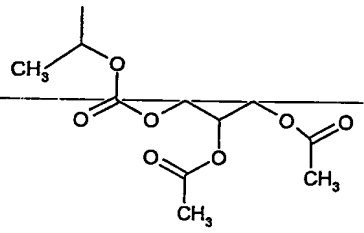
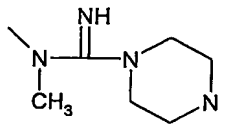
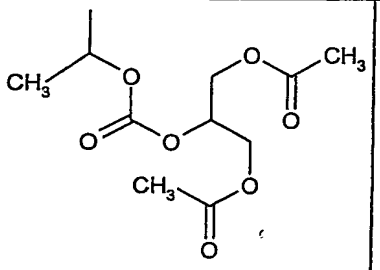
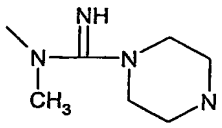
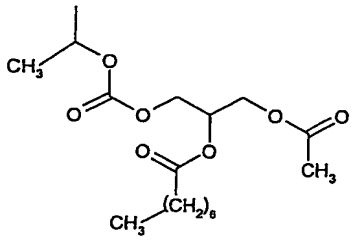
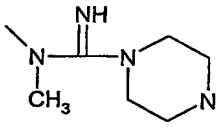
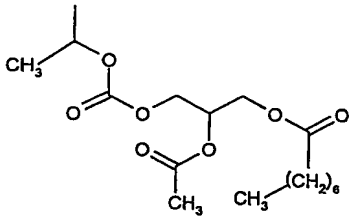
To 24.5 g of 7-{2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-[(Z)-fluoromethoxyimino]-acetylamino}-3-formyl-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 1-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxycarbonyloxy)-ethyl ester in 950 ml of dimethylacetamide 12.2 g of N-amino N-methyl-piperazine-1-carboxamidine, 19.4 ml of 2N HCl and 45 ml of water are added. A reaction mixture formed is allowed to stand at ambient temperature. A residue obtained after concentration is triturated with ether and cooled. 150 ml of HCl-saturated ether are added and a mixture formed is stirred. Ether is decanted, a residue obtained is washed and after drying optionally purified, e.g. chromatographed. 7-{2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-(fluoro-methoxyimino)-acetylamino}-3-formyl-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 1-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxycarbonyloxy)-ethyl ester is obtained.

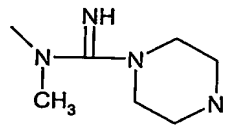
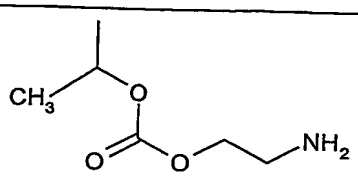
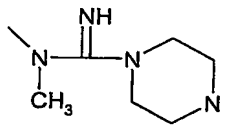
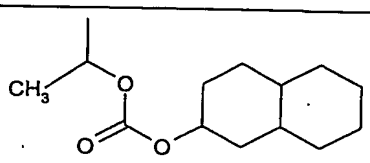
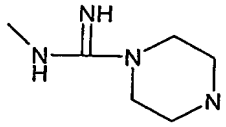
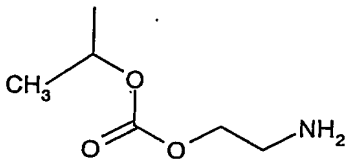
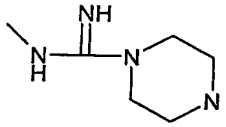
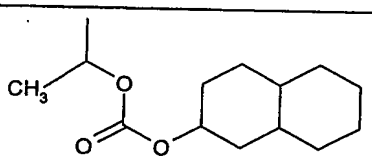
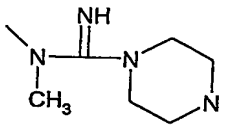
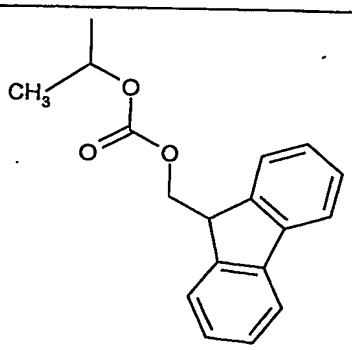
^{1}H-NMR (DMSO-d_6): 1.53 (d, 3H, J=6Hz); 3.21 (bs, 1H); 3.27-3.38 (m, 4H); 3.61 (2xd, 1H, J=18Hz); 3.64-3.74 (m, 7H); 3.99 (m, 1H); 4.18 (m,1H); 4.31/4.35 (2xd, 1H, J=18Hz); 5.29-5.34 (2xd, 1H, J=5Hz); 5.72 (m, 1H); 5.83 (m, 1H,); 5.94-6.01 (2xq, 1H, J=5Hz, 8Hz); 6.84-6.94 (2xq, 1H, J=5Hz); 7.91/7.94 (2xs, 1H); 8.23 (s, 2H); 9.01 (bs, 1H); 9.25 (bs, 1H); 9.62 (bs, 2H); 9.82 (2xd, 1H, J=8Hz)

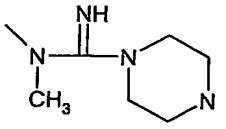
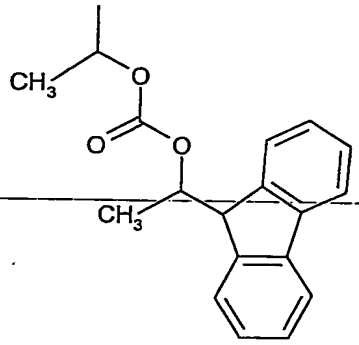
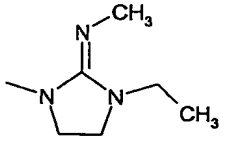
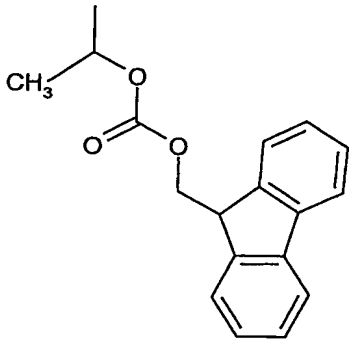
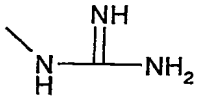
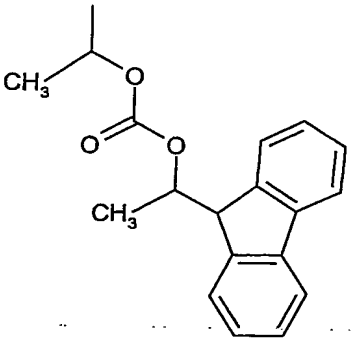
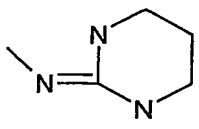
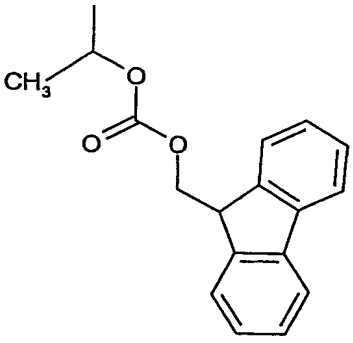
In the manner as described in Example 2, but using the appropriate starting materials the following compounds are obtained. Purification may be carried out optionally.

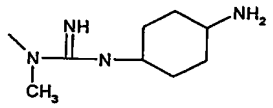
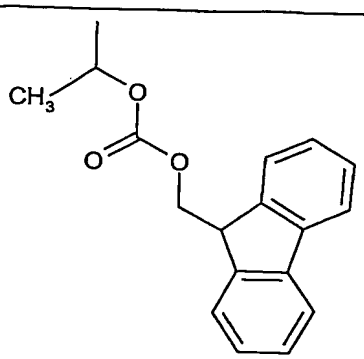
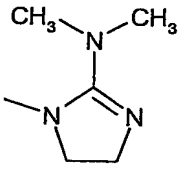
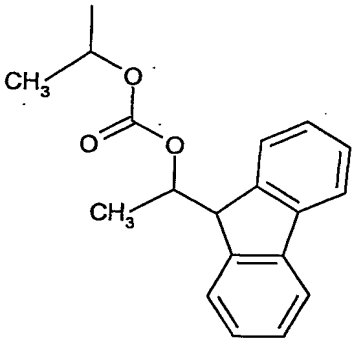
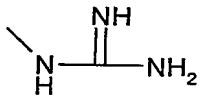
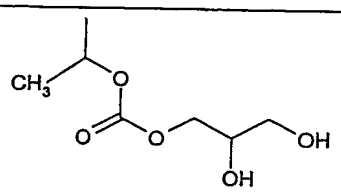
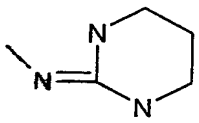
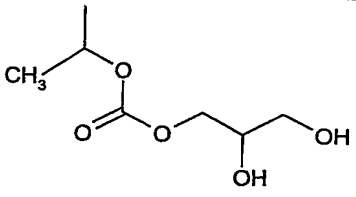
TABLE 1

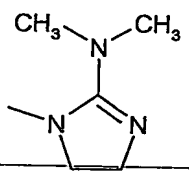
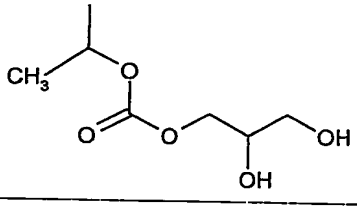
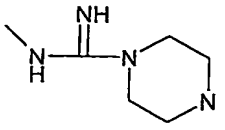
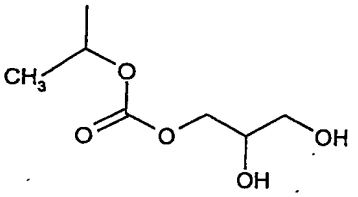
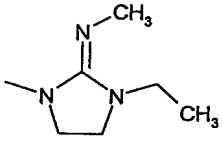
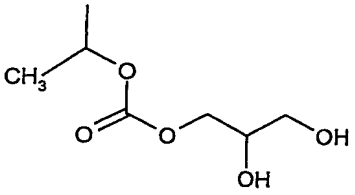
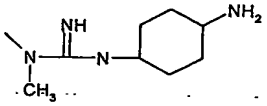
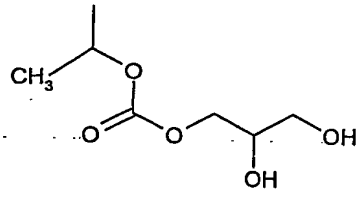


Ex.	R_1	R_2	^{1}H-NMR (d_6-DMSO)
3			1.56 (d, 3H, J=6Hz); 2.06 (2xs, 6H); 3.26 (bs, 3H); 3.37 (bs, 4H); 3.62-3.65 (m, 1H); 3.73 (m, 4H); 4.13-4.39 (m, 5H); 5.20 (m, 1H); 5.33-5.35 (m, 1H,); 5.72 (bs, 1H); 5.85 (bs, 1H), 5.99 (m, 1H,); 6.89-6.98 (m, 1H,); 8.02 (2xs, 1H); 9.03 (bs, 1H); 9.25 (bs, 1H); 9.67 (bs, 2H,); 9.85 (d, 1H, J=8Hz)
4			1.58 (d, 3H, J=6Hz); 2.03 (2xs, 6H); 3.28 (m, 4H); 3.30 (bs, 3H); 3.63 (d, 1H, J=18Hz); 3.72 (m, 4H); 4.13-4.33 (m, 4H); 4.39 (d, 1H, J=18Hz); 5.06-5.22 (m, 1H); 5.32 (d, 1H, J=5Hz); 5.73 (m, 1H); 5.86 (m, 1H), 6.00 (dd, 1H, J=6Hz, 9Hz); 6.98 (m, 1H,); 8.05 (s, 1H); 8.27 (bs, 2H); 9.04 (bs, 1H); 9.28 (bs, 1H); 9.64 (bs, 2H,); 9.84 (m, 1H)
5			0.87 (t, 3H, J=6Hz); 1.25 (m, 8H); 1.50 (m, 2H); 1.56 (d, 3H, J=6Hz); 2.03 (2xs, 3H); 2.30 (m, 2H); 3.25 (m, 4H); 3.30 (m, 3H); 3.58-3.62 (m, 1H,); 3.72 (m, 4H); 4.16-4.35 (m, 4H); 4.38-4.41 (m, 1H,); 5.05-5.20 (m, 1H); 5.30-5.35 (2xd, 1H, J= 6Hz); 5.73 (m, 1H); 5.83 (m, 1H), 6.00 (m, 1H,); 6.90-6.98 (2xq, 1H, J=6Hz); 7.98-8.03 (2xs, 1H); 8.27 (m, 2H); 9.03 (bs, 1H); 9.30 (bs, 1H); 9.67 (bs, 2H,); 9.87 (m, 1H)
6			0.87 (t, 3H, J=7Hz); 1.25 (m, 8H); 1.52 (m, 2H); 1.57 (d, 3H, J=6Hz); 2.22 (2xs, 3H); 2.30 (t, 2H, J=7Hz); 3.27 (m, 4H); 3.33 (bs, 3H); 3.63 (m, 1H,); 3.73 (m, 4H); 4.12-4.41 (m, 5H); 5.20 (m, 1H); 5.33 (2xd, 1H, J=6Hz); 5.73 (bs, 1H); 5.85 (bs, 1H), 5.97-6.03 (m, 1H,); 6.88-6.99 (m, 1H); 7.98-8.06 (m, 1H); 8.28 (bs, 2H); 9.06 (bs, 1H); 9.30 (bs, 1H); 9.67 (bs, 2H,); 9.85 (t, 1H, J=8Hz)

7			1.56 (d, 3H, J=6Hz); 3.10 (m, 2H); 3.20 (m, 4H); 3.30 (2xs, 3H); 3.60 (m, 1H); 3.72 (m, 4H); 4.32 (m, 3H); 5.32 (2xd, 1H, J=5Hz); 5.70 (bs, 1H); 5.83 (bs, 1H), 5.97 (m, 1H); 6.90-6.98 (2xq, 1H, J=6Hz); 7.96 (2xs, 1H); 8.25 (bs, 2H); 8.30 (bs, 2H); 9.10 (bs, 1H); 9.30 (bs, 1H); 9.70 (bs, 2H,); 9.73 (m, 1H)
8			1.25-1.85 (m, 16H); 1.56 (d, 3H, J=6Hz); 3.15 (m, 4H); 3.27 (2xs, 3H); 3.60 (m, 1H); 3.62 (m, 4H); 4.37 (d, 1H, J=17Hz); 4.57 (m, 1H); 5.19/5.36 (2xd, 1H, J=6Hz); 5.73-5.87 (m, 2H); 5.99 (m, 1H,); 6.60-6.98 (2xm, 1H); 7.40/7.72 (2xm, 1H); 8.25 (m, 3H); 9.85-9.92 (m, 1H)
9			1.56 (2xd, 3H, J=6Hz); 3.10-3.90 (m, 8H); 3.20 (m, 2H); 3.53 (m, 1H); 4.33 (m, 2H); 4.63 (m, 1H); 5.31 (2xd, 1H, J=5Hz); 5.70 (m, 1H); 5.82 (m, 1H), 5.93-6.02 (2xdd, 1H, J=5Hz, 8Hz); 6.72-6.97 (2xq, 1H, J=6Hz); 8.25 (m, 2H); 8.60-8.70 (2xs, 1H); 9.75 (bs, 2H); 9.80 (2xd, 1H,J=8Hz)
10			1.20-1.87 (m, 16H); 1.56 (d, 3H, J=6Hz); 3.15-3.47(m, 8H); 3.55 (d, 1H, J=18Hz); 4.75 (m, 1H); 5.30 (2xd, 1H, J=5Hz); 5.72 (m, 1H); 5.83 (m, 1H); 6.02 (2xm, 1H,); 6.85/6.95 (2xm, 1H); 8.52/8.62 (2xs, 1H); 9.70 (m, 1H)
11			1.49 (d, 3H, J=5Hz); 3.21 (bs, 3H); 3.30-3.70 (m, 8H); 3.60 (d, 1H, J=18Hz); 4.30 (m,1H); 4.31 (d, 1H, J=18Hz); 4.60 (m, 2H); 5.30 (2xd, 1H, J=5Hz); 5.69 (m, 1H); 5.83 (m, 1H,); 5.92-6.02 (2xm, 1H); 6.82/6.91 (2xq, 1H, J=5Hz); 7.33 (m, 2H); 7.42 (m, 2H); 7.62 (m, 2H); 7.88 (m, 2H); 7.93 (s, 1H); 8.22 (bs, 1H); 8.98 (bs, 1H); 9.22 (bs, 1H); 9.63 (bs, 1H); 9.83 (2xd, 1H, J=8Hz)

12			0.72-0.84 (3xd, 3H, J=6Hz); 1.45-1.63 (3xd, 3H, J=6Hz); 3.30-3.70 (m, 8H); 3.33 (4xs, 3H); 3.62 (d, 1H, J=18Hz); 4.33 (d, 1H, J=18Hz); 4.43 (m,1H); 5.20-5.99 (m, 5H); 6.65-7.00 (3xq, 1H, J=6Hz); 7.30-8.30 (m, 9H); 9.03-9.30 (m, 3H); 9.83-9.93 (m, 2H)
13			1.20 (2xt, 3H, J=7Hz); 1.51 (d, 3H, J=5Hz); 3.19 (s, 3H); 3.53-3.83 (m, 7H); 4.29-4.40 (m,2H); 4.53-4.68 (m, 2H); 5.33 (2xd, 1H, J=5Hz); 5.72 (m, 1H); 5.83 (m, 1H,); 5.93/6.01 (2xdd, 1H, J=5Hz, 8Hz); 6.83/6.91 (2xq, 1H, J=5Hz); 7.31-7.39 (m, 2H); 7.40-7.46 (m, 2H); 7.62-7.68 (m, 3H); 7.88-7.92 (m, 2H); 8.23 (bs, 1H); 8.62 (bs, 1H); 9.85 (2xd, 1H, J=8Hz)
14			1.50 (d, 3H, J=6Hz); 3.55 (d, 1H, J=18Hz); 4.33 (t,1H, J=6Hz); 4.57 (d, 1H, J=18Hz); 4.64 (m, 2H); 5.31 (2xd, 1H, J=5Hz); 5.71 (m, 1H); 5.82 (m, 1H,); 5.93/6.02 (2xdd, 1H, J=5Hz, 8Hz); 6.71/6.91 (2xq, 1H, J=6Hz); 7.31-7.48 (m, 4H); 7.65 (m, 2H); 7.80 (bs, 2H); 7.95 (m, 2H); 8.25-8.30 (2xs, 1H); 8.27 (bs, 2H); 9.85 (2xd, 1H, J=8Hz); 12.10 (bs, 1H)
15			1.52 (d, 3H, J=6Hz); 1.90 (m, 2H); 3.35 (m, 4H); 3.55 (d, 1H, J=18Hz); 4.32 (t,1H, J=6Hz); 4.59 (2xd, 1H, J=18Hz); 4.62 (m, 2H); 5.31 (2xd, 1H, J=5Hz); 5.71 (m, 1H); 5.83 (m, 1H,); 5.91/6.01 (2xdd, 1H, J=5Hz, 8Hz); 6.80/6.90 (2xq, 1H, J=6Hz); 7.32-7.43 (m, 4H); 7.63 (m, 2H); 7.90 (m, 2H); 8.35 (s, 1H); 8.45 (s, 1H); 9.85 (2xd, 1H, J=8Hz)

16			1.50-1.59 (m,4H); 1.52 (d, 3H, J=6Hz); 1.92-2.03 (m, 4H); 2.94 (m, 1H); 3.27 (2xs, 3H); 3.57 (d, 1H, J=18Hz); 3.63 (m, 1H); 4.32 (m,1H); 4.53-4.68 (m, 3H); 5.32 (2xd, 1H, J=5Hz); 5.72 (m, 1H); 5.83 (m, 1H,); 5.95/6.01 (2xdd, 1H, J=5Hz, 8Hz); 6.84/6.91 (2xq, 1H, J=6Hz); 7.31-7.38 (m, 2H); 7.42-7.47 (m, 2H); 7.63 (m, 2H); 7.89 (m, 2H); 7.91 (2xs, 1H); 8.05 (bs, 1H); 8.20 (bs, 2H); 8.27 (s, 2H); 8.48 (bs, 1H); 9.85 (2xd, 1H, J=8Hz)
17			1.51 (2xd, 3H, J=6Hz); 3.23 (bs, 6H); 3.59 (m, 2H); 3.68 (m, 1H,); 3.88 (m, 2H); 4.05 (d, 1H; J=18Hz); 4.34 (m, 1H); 4.62 (m, 2H); 5.32 (2xd, 1H, J=5Hz); 5.73 (m, 1H); 5.85 (m, 12H); 5.96/6.02 (2xdd, 1H, J=5Hz, 8Hz); 6.84/6.92 (2xq, 1H J=6Hz); 7.37 (m, 2H); 7.42 (m, 2H); 7.65 (m, 2H); 7.90 (m, 2H); 8.24 (bs, 1H); 9.30 (bs, 1H); 9.87 (2xd, 1H, J=8Hz)
18			1.56 (d, 3H, J=6Hz); 3.38 (m, 1H); 3.57 (d, 1H, J=18Hz); 3.68 (m, 2H); 3.99 (ABX-system, 1H, J_{AB}=10Hz, J_{AX}=6Hz); 4.22 (ABX-system, 1H, J_{AB}=10Hz, J_{BX}=5Hz); 4.55 (d, 1H, J=18Hz); 5.31 (2xd, 1H, J=5Hz); 5.73 (m, 1H); 5.83 (m, 1H,); 5.97 (dd, 1H, J=5Hz, 8Hz); 6.95 (q, 1H, J=5Hz); 8.21 (s, 2H); 8.30 (s, 1H); 9.82 (d, 1H, J=8Hz); 12.05 (s, 1H)
19			1.56 (2xd, 3H, J=6Hz); 1.90 (m, 2H); 3.29-3.39 (m, 5H); 3.55 (d, 1H, J=18Hz); 3.69 (m, 2H); 4.00 (m, 1H); 4.20 (m, 1H); 4.57 (2xd, 1H, J=18Hz); 4.75 (m, 1H); 5.08 (m, 1H); 5.33 (2xd, 1H, J=5Hz); 5.71 (m, 1H); 5.85 (m, 1H,); 5.95/6.02 (2xdd, 1H, J=5Hz, 8Hz); 6.85/6.92 (2xq, 1H, J=6Hz); 8.25 (s, 1H); 8.42 (s, 1H); 9.85 (2xd, 1H, J=8Hz); 12.06 (bs, 1H)

20			1.57 (2xd, 3H, J=6Hz); 3.20 (2xs, 3H); 3.28-3.40 (m, 7H); 3.66 (m, 1H,); 3.72 (m, 2H); 3.93 (m, 1H); 4.02-4.08 (m, 2H); 4.20 (m, 1H); 5.31 (2xd, 1H, J=5Hz); 5.70-5.89 (m, 2H); 5.95/6.03 (m, 1H); 6.81/6.98 (m, 1H); 7.73 (m, 1H); 8.12-8.22 (m, 4H); 9.82 (2xd, 1H, J=8Hz)
21			1.50 (2xd, 3H, J=6Hz); 3.20-3.80 (m, 12H); 3.93 (m, 1H); 4.13 (m, 1H); 4.57/4.62 (2xd, 1H, J=18Hz); 5.23-5.34 (2xd, 1H, J=5Hz); 5.66 (m, 1H); 5.80 (m, 1H,); 5.90-5.98 (2xq, 1H, J=5Hz, 8Hz); 6.78/6.84 (2xq, 1H, J=5Hz); 8.20 (s, 2H); 8.48/8.59 (2xs, 1H); 8.50 (bs, 1H); 9.58 (bs, 2H); 9.78 (2xd, 1H, J=8Hz); 12.20/12.31 (2xbs, 1H)
22			1.21 (2xt, 3H, J=7Hz); 1.56 (2xd, 3H, J=7Hz); 3.18 (bs, 3H); 3.30-3.42 (m, 2H); 3.57-3.71 (m, 4H); 3.80-3.88 (m, 4H); 3.94 (m, 1H); 3.98-4.07 (m, 1H); 4.17-4.22 (m, 1H); 4.76 (m, 1H); 5.07 (t, 1H, J=5Hz); 5.36 (2xd, 1H, J=5Hz); 5.74 (m, 1H); 5.86 (m, 1H,); 6.01 (m, 1H); 6.88/6.96 (2xq, 1H, J=5Hz); 7.71 (2xs, 1H); 8.25 (bs, 2H); 8.58 (bs, 1H); 9.85 (2xd, 1H, J=8Hz)
23			1.50-1.59 (m,4H); 1.52 (d, 3H, J=6Hz); 1.92-2.03 (m, 4H); 2.92 (m, 1H); 3.25 (m, 1H); 3.27 (2xs, 3H); 3.50 (m, 1H); 3.57 (d, 1H, J=18Hz); 3.63 (m, 2H); 3.96 (m, 1H); 4.21 (m, 1H); 4.62 (d, 1H, J=18Hz); 5.27 (2xd, 1H, J=5Hz); 5.72 (m, 1H); 5.83 (m, 1H,); 5.95/6.01 (2xdd, 1H, J=5Hz, 8Hz); 6.84/6.91 (2xq, 1H, J=6Hz); 7.91 (s, 1H); 8.05 (bs, 1H); 8.20 (bs, 2H); 8.27 (s, 2H); 8.48 (bs, 1H); 9.85 (2xd, 1H, J=8Hz)

Example 24:

3-Carbamoyloxymethyl-7-{2-furan-2-yl-2-[(Z)-methoxyimino]-acetylamino}-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 1-(9H-fluoren-9-yl-methoxycarbonyloxy)-ethyl ester

To 41.5 g of cefuroximsodium salt in 840 ml of dimethylacetamide 38 g of carbonic acid 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester 1-iodo-ethyl ester in 200 ml of dimethylacetamide are added. The reaction mixture is stirred, poured into 2 l of an ice-water mixture and extracted with ethyl acetate. An organic layer is washed with saturated sodium bicarbonate solution, brine, dried, concentrated and the residue triturated with ether.

^{1}H-NMR (DMSO-d_6): 1.48 (d, 3H, J=6Hz); 3.55 (d, 1H, J=18Hz); 3.64 (2xd, 1H, J=18Hz); 3.89 (2xs, 3H); 4.31-4.38 (m,1H); 4.49-4.86 (m, 4H); 5.22 (2xd, 1H, J=5Hz); 5.58-5.89 (m, 1H); 6.60-6.73 (m, 2H); 6.78/6.89 (2xq, 1H, J=6Hz); 7.32-7.38 (m, 2H); 7.42-7.46 (m, 2H); 7.62-7.68 (m, 2H); 7.83 (m, 1H); 7.92 (m, 2H); 9.79 (2xd, 1H, J=8Hz)

Analogously to example 24 but using the appropriate starting materials the following compound is prepared.

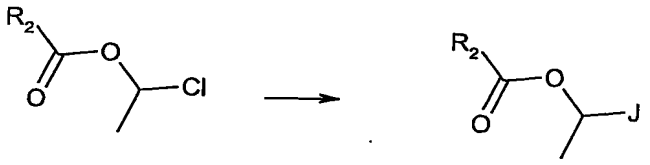
Example 25:

3-Carbamoyloxymethyl-7-{2-furan-2-yl-2-[(Z)-methoxyimino]-acetylamino}-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 1-(2,3-dihydroxy-propoxycarbonyloxy)-ethyl ester

^{1}H-NMR (DMSO-d_6): 1.50 (d, 3H, J=6Hz); 3.30 (m, 2H); 3.49/ 3.62 (2xd, 1H, J=18Hz); 3.63 (m, 1H); 4.00 (s, 3H); 4.03 (m, 1H); 4.18 (m, 1H); 4.75/4.80 (m, 1H); 5.18-5.24 (2xd, 1H, J=5Hz); 5.80-5.87 (m, 1H); 6.67 (m, 1H); 6.78/6.87 (2xq, 1H, J=6Hz); 7.22 (d, 1H, J=3.5Hz); 7.83 (m, 1H); 9.57 (2xd, 1H, J=8Hz)

Example 26: Intermediates according to scheme 1

R_2 is as described in TABLE 1



(1) (2)

Ex*	Chloride (1) ^{1}H-NMR ($CDCl_3$)	Iodide (2) ^{1}H-NMR ($CDCl_3$)
3´	1.86 (d, 3H, J=6Hz); 2.11 (s, 3H); 2.20 (s, 3H); 4.20 (m, 1H); 4.34 (m, 2H); 4.44 (m, 1H); 5.28 (m, 1H); 6.43 (2xq,1H, J=6Hz)	2.08 (s, 3H); 2.12 (s, 3H); 2.25 (d, 3H, J=6Hz); 4.18 (m, 1H); 4.30 (m, 2H); 4.42 (m, 1H); 5.24 (m, 1H); 6.74 (2xq, 1H, J=6Hz)
4´	1.84/1.86 (2xd, 3H, J=6Hz); 2.08-2.10 (4xs, 6H); 4.17-4.40 (m, 2H); 5.14-5.28 (m, 1H); 6.41-6.42 (2xq,1H, J=6Hz)	2.10 (2xs, 3H); 2.27 (d, 3H, J=6Hz); 4.18 (m, 2H); 4.35 (m, 2H); 5.18-5.28 (m, 1H); 6.74 (2xq, 1H, J=6Hz)

5´	0.90 (t, 3H, J=6Hz); 1.30 (m, 8H); 1.63 (m, 2H); 1.87 (d, 3H, J=6Hz); 2.10 (s, 3H); 2.34 (t, 2H, J=7Hz); 4.20 (m, 2H); 4.38 (m, 2H); 5.20 (m, 1H); 6.44 (q,1H, J=6Hz)	0.90 (t, 3H, J=6Hz); 1.32 (m, 8H); 1.64 (m, 2H); 2.10 (s, 3H); 2.28 (d, 3H, J=6Hz); 2.36 (m, 2H); 4.20 (m, 2H); 4.38 (m, 2H); 5.20 (m, 1H); 6.78 (q,1H, J=6Hz)
6´	0.87 (t, 3H, J=6Hz); 1.28 (m, 8H); 1.62 (m, 2H); 1.84 (d, 3H, J=6Hz); 2.10 (s, 3H); 2.32 (m, 2H); 4.30 (m, 2H); 4.42 (m, 2H); 5.23 (m, 1H); 6.40 (q,1H, J=6Hz)	0.87 (t, 3H, J=6Hz); 1.28 (m, 8H); 1.62 (m, 2H); 2.10 (s, 3H); 2.24 (d, 3H, J=6Hz); 2.32 (m, 2H); 4.18 (m, 2H); 4.30 (m, 2H); 5.23 (m, 1H); 6.74 (q,1H, J=6Hz)
7´	1.44 (s, 9H); 1.83 (d, 3H, J=6Hz); 3.44 (m, 2H); 4.27 (t, 2H, J=5Hz);); 6.42 (q,1H, J=6Hz)	1.44 (s, 9H); 2.24 (d, 3H, J=6Hz); 3.44 (m, 2H); 4.27 (t, 2H, J=5Hz); 6.76 (q,1H, J=6Hz)
8´	0.90-1.97 (m, 16H); 1.82 (d, 3H, J=6Hz); 4.60 (m,1H); 6.42 (q, 1H, J=6Hz)	0.90-1.97 (m, 16H); 2.27 (d, 3H, J=6Hz); 4.64 (m,1H); 6.79 (q, 1H, J=6Hz)
9´	see ex. 7	see ex. 7
10´	see ex. 8	see ex. 8
11´	1.87 (d, 3H, J=6Hz); 4.28 (t, 1H, J=7Hz); 4.42 (dd, 1H, J=7Hz, 10Hz); 4.52 (dd, 1H, J=7Hz, 10Hz); 6.46 (q, 1H, J=6Hz); 7.32 (m, 2H); 7.42 (m, 2H); 7.61 (m, 2H); 7.77 (m, 2H)	2.28 (d, 3H, J=6Hz); 4.28 (t, 1H, J=7Hz); 4.40 (dd, 1H, J=7Hz, 10Hz); 4.53 (dd, 1H, J=7Hz, 10Hz); 6.70 (q, 1H, J=6Hz); 7.32 (m, 2H); 7.42 (m, 2H); 7.61 (m, 2H); 7.78 (m, 2H)
12´	0.78/0.81 (sxd, 3H, J=6Hz); 1.93/1.94 (2xd, 3H, J=6Hz); 4.39/4.43 (sxd, 1H, J=4Hz); 5.57 (m, 1H); 6.55/6.56 (2xq, 1H, J=6Hz); 7.34 (m, 2H); 7.42 (m, 2H); 7.57 (m, 1H); 7.72 (m, 1H); 7.79 (m, 2H)	0.76/0.89 (sxd, 3H, J=6Hz); 2.21/2.23 (2xd, 3H, J=6Hz); 4.379/4.40 (2xd, 1H, J=4Hz); 5.56 (m, 1H); 6.86/6.88 (2xq, 1H, J=6Hz); 7.30 (m, 2H); 7.40 (m, 2H); 7.52 (m, 1H); 7.70 (m, 1H); 7.73 (m, 2H)
13´	see ex. 11	see ex. 11
14´	see ex. 11	see ex. 11
15´	see ex. 11	see ex. 11
16´	see ex. 11	see ex. 11
17´	see ex. 11	see ex. 11
18´	see ex. 1a	see ex. 1b
19´	see ex. 1a	see ex. 1b
20´	see ex. 1a	see ex. 1b
21´	see ex. 1a	see ex. 1b
22´	see ex. 1a	see ex. 1b
23´	see ex. 1a	see ex. 1b
24´	see ex. 11	see ex. 11
25´	see ex. 1a	see ex. 1b

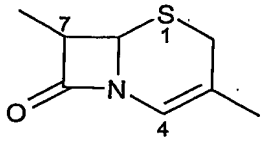
Ex* : Intermediates of a compound to the corresponding example number

Patent claims:

1. A carboxylic acid ester of a pharmaceutically active compound having a carboxylic acid group –COOH as a part of its chemical structure, which ester is selected from the group consisting of 1-(1,3-disubstituted propoxycarbonyloxy)-ethyl carboxylic acid ester, 1-(2,3)-disubstituted propoxycarbonyloxy)-ethyl carboxylic acid ester, 1-(9H-fluorene-9-yl-(C_{1-4})alkanyloxycarbonyloxy)-ethyl carboxylic acid ester, 1-(decahydro-naphthalene-2-yl-oxycarbonyloxy)-ethyl carboxylic acid ester and 1-(2-amino(C_{1-6})alkoxy-carbonyloxy)-ethyl carboxylic acid ester.

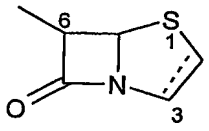
2. A carboxylic acid ester according to claim 1 wherein the pharmaceutically active compound is an antibiotic, e.g. selected from the group consisting of β-lactam antibiotics.

3. A carboxylic acid ester according to any one of claims 1 or 2 wherein said ester is an ester of the carboxylic group attached in position 4 of the azabicyclo-[4,2,0]octene ring structure of a cephalosporin, e.g. of formula



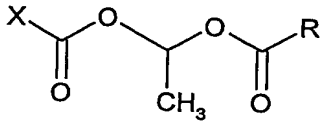
I

or an ester of the carboxylic acid group attached in position 3 of the azabicyclo-[3,2,0]heptene ring structure of a penicillin, e.g. of formula



II

4. A carboxylic acid ester according to any one of claims 1 to 3 of formula



III

wherein X is a group of formula I or II and R is

- a mono-or disubstituted 1-propoxy or 2-propoxy substituted with OH and/or (C_{1-22})alkyl-carbonyloxy,
- 9H-fluorene-9-yl-(C_{1-4})alkoxy,

- decahydronaphthoxy or
- amino(C_{1-6})alkoxy.

5. A carboxylic acid ester according to any one of claims 1 to 4 wherein said ester is an ester selected from the group consisting of 1-(2,3,-dihydroxy-propoxycarbonyloxy)-ethyl carboxylic acid ester, 1-(2,3-diacetoxy-propoxycarbonyloxy)-ethyl carboxylic acid ester, 1-(3-acetoxy-2-octanoyl-oxy-propoxycarbonyloxy)-ethyl carboxylic acid ester, 1-(2-acetoxy-3-octanoyloxy-propoxy-carbonyloxy)-ethyl carboxylic acid ester, 1-(2-acetoxy-1-acetoxymethyl-ethoxy-carbonyloxy)-ethyl carboxylic acid ester, 1-(9H-fluorene-9-yl-methoxycarbonyloxy)-ethyl carboxylic acid ester, 1-(9H-fluorene-9-yl-ethoxycarbonyloxy)-ethyl carboxylic acid ester, 1-(decahydro-naphthalene-2-yl-oxycarbonyloxy)-ethyl carboxylic acid ester and 1-(2-amino-ethoxy-carbonyloxy)-ethyl carboxylic acid ester of the carboxylic acid attached in position 4 of the ring structure of a cephalosporin of formula I or of the carboxylic acid attached in position 3 of the ring structure of a penicillin of formula II.

6. A carboxylic acid ester according to any one of claims 1 to 5 in the form of a salt.

7. A carboxylic acid ester according to any one of claims 1 to 6 for use as a pharmaceutical.

8. A carboxylic acid ester according to any one of claims 1 to 6 for the preparation of a medicament for the treatment of microbial diseases.

9. A pharmaceutical composition comprising a carboxylic acid ester according to any one of claims 1 to 6 in association with at least one pharmaceutically acceptable excipient.

Abstract

A carboxylic acid ester of a pharmaceutically active compound having a carboxylic acid group –COOH as a part of its chemical structure, which ester is selected from the group consisting of 1-(1,3-disubstituted propoxycarbonyloxy)-ethyl carboxylic acid ester, 1-(2,3)-disubstituted propoxycarbonyloxy)-ethyl carboxylic acid ester, 1-(9H-fluorene-9-yl-(C_{1-4})alkanyloxycarbonyloxy)-ethyl carboxylic acid ester, 1-(decahydro-naphthalene-2-yl-oxycarbonyloxy)-ethyl carboxylic acid ester and 1-(2-amino(C_{1-6})alkoxy-carbonyloxy)-ethyl carboxylic acid ester.

PCT Application

PCT/EP2004/000683